

AD _____

Award Number: DAMD17-94-J-4327

TITLE: Breast Cancer Screening by Physical Examination:
Randomized Trial in the Phillipines

PRINCIPAL INVESTIGATOR: D.M. Parkin, M.D.

CONTRACTING ORGANIZATION: International Agency for Research on Cancer
69372 Lyon Cedex 08, France

REPORT DATE: October 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE October 1999	3. REPORT TYPE AND DATES COVERED Annual (30 Sep 98 - 29 Sep 99)	
4. TITLE AND SUBTITLE Breast Cancer Screening by Physical Examination: Randomized Trial in the Philippines			5. FUNDING NUMBERS DAMD17-94-J-4327	
6. AUTHOR(S) D.M. Parkin, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) (International Agency for Research on Cancer) 69372 Lyon Cedex 08, France e-mail:			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release distribution unlimited				12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words) Completed activities. Data entry, checking and cleaning of several data bases, which will be the bases for the follow up and evaluation of the intervention have been completed. Master file Nominal list of all women interviewed and offered PE. Includes 10% who refused PE 154,000 Referrals Nominal list of all women detected positive at 1 st PE by nurses. This file contains also the details of clinical follow up and final diagnosis. 3,492 Intervention Lists of the eligible population resident in the intervention HCs in the years when the intervention 218,928 population lists was conducted. Control population Lists of the eligible population resident in the control HCs in the years when the intervention was 191,086 lists conducted. Repeated exams Outcome of two examinations performed an year apart in a subgroup of the intervention cohort. 3,000 On-going Interview of a sample of 1,000 women resident in the control areas. Six hundred and seventy eight interviews had been completed and processed by the end of August 1999. Women positive at PE who did not comply with clinical follow-up are being approached by project doctors a second time as a further attempt to improve clinical follow up. Cancer registry follow-up procedures have been established and breast cancer cases are recorded regularly. Death certificates (all causes) of women resident in Metro Manila are collected regularly.				
14. SUBJECT TERMS Breast Cancer, Screening, Physical Examination				15. NUMBER OF PAGES 19
				16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

- ☒ Where copyrighted material is quoted, permission has been obtained to use such material.
- ☐ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.
- ☐ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.
- ☐ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).
- ☒ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.
- ☐ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.
- ☐ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.
- ☐ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.


PI - Signature

24/9/99
Date

(4) TABLE OF CONTENTS

	Page
Front page.....	1
SF 298 Report Documentation Page	2
Foreword	3
Table of contents	4
Introduction	5
Body	7
Key research accomplishments	13
Reportable outcomes	13
Conclusions	14
Tables	15-17
References	18

(5) **INTRODUCTION**

In 1990 breast cancer accounted for 795,000 new cases per year (Ferlay *et al.*, 1998), and it was the most frequent cancer in women. Incidence rates are still rising in many countries, particularly in the developing world (Coleman and Estève, 1993). It seems that these trends are likely to continue, since the current pattern of later childbearing, decreasing fertility, and 'westernization' of diets will all be associated with increased risk.

At present, our knowledge of environmental risk factors does not permit formulation of any practical primary prevention programs. The introduction of adjuvant therapy with Tamoxifen has improved survival of older cases and a decline of mortality from breast cancer below age 50, observed in some high-risk countries, has also been attributed to adjuvant therapy (Nab *et al.*, 1994, Olivotto *et al.*, 1994). However, further improvements in surgical techniques, or in radiotherapy, are very unlikely to provide more than marginal changes in mortality rates.

A much greater decrease in deaths from breast cancer is achievable through screening programs which lead to detection of cancers which are smaller, at an earlier stage, and less malignant than those which surface clinically. Several randomized trials of screening for breast cancer have been carried out; in the majority the screening modality used was mammography, with or without physical examination of the breasts. There is a clear consensus that such screening programs are capable of decreasing the risk of mortality from breast cancer in women aged 50 or older (Miller *et al.*, 1990; Day, 1991; Moss, 1996). The efficacy of mammography in women below 50 is still a very controversial issue resulting in contradictory recommendations and policies (Moss, 1996; Nelson, 1997). At best, mortality reduction in this age group would be only 15% or one-half that of older women (based on meta-analyses of randomized trials). The reason of lower efficiency of mammography in younger women is not clear; possible causes are cancers growing faster in these ages or sensitivity of mammography in the pre-menopausal breast being relatively low.

Population screening programs which depend upon mammography require extensive provision of expensive technology and highly trained radiologists and radiographers. The cost per life-year saved is therefore relatively high (Barnum and Greenberg, 1991), and clearly an inappropriate use of health care resources for many countries (WHO, 1984).

The alternative screening strategies which have been proposed are physical examination of the breasts (PE), and breast self-examination (BSE). Short-term results of a large scale trial of BSE among 300,000 textile workers in Shanghai, China, conducted by researchers of the University of Washington have been recently published (Thomas *et al.*, 1997). Biases such as low compliance with the intervention, failure of proper randomization or low proficiency in performing BSE could be confidently excluded. No significant reduction of breast cancer mortality in the intervention group has been detected after 5 years of follow-up and the distribution of stage at diagnosis in screen and control groups were very similar. As discussed by the Authors, both results are not definitive; even in trials of

mammography a reduction of mortality appeared only after 5 years from entry into the study and stage at diagnosis, which is assessed retrospectively, may well be affected by a rate of mis-classification which can obscure existing differences in the intervention and control groups.

Nevertheless, the small size of the lesions diagnosed in the control subjects in this trial (47 % ≤ 2 cm diameter) suggests a high level of health-awareness in the Shanghai population, and may give little scope for improvement in outcome through early detection by BSE.

At present PE has never been used as the sole modality of screening, so that its effectiveness is not known. Indirect evidence based on estimates of the accuracy of PE relative to mammography suggests that this type of examination could reduce mortality rates by 2/3 to 3/4 of that achievable by mammography screening in women aged 50 or more. PE alone may be effective in younger women, among whom up to 25% cancers are missed by mammography; in addition, there is evidence that PE improves the performance of mammography. The working group who reviewed in 1979 the results of the Breast Cancer Detection Demonstration Project, the first large non-experimental evaluation of mammography, stated that high priority should be given to the evaluation of PE as a single screening modality. The recommendation was not followed by action until the project described here, possibly because of the rapid spreading of mammography in most developed countries which vitiated the feasibility of an unscreened control group.

The purpose of the present work was to establish 1) whether a program of mass screening by PE performed by trained paramedical personnel could be set up in a developing country as part of the routine activity of first level health services, and 2) whether and to what extent such a program could reduce mortality from breast cancer. The location is Metro Manila and Rizal Province of the Philippines. This population has a relatively high incidence of breast cancer, considerably above that of other Asian populations, and comparable to that in southern Europe.

(6) **BODY**

The study is a randomized controlled trial of the effect of annual physical examination (PE) of the breasts performed by trained nurses/midwives, in reducing mortality from breast cancer. The study area comprises the central, more urbanized municipalities of the National Capital Region (Districts I, II, III and IV), which includes 12 municipalities each having municipal health centers in the township area and barangay health stations in more rural areas. In 1990, the estimated size of the female population aged 35-64 was about 340,000. The units of randomization are health centers (HCs) within the selected municipalities of the Manila - Rizal area.

Women aged 35-64 years resident in the intervention HC areas were offered annual breast examinations, carried out by specialized midwives/nurses. At the first visit, these women were also instructed in the technique of breast self-examination (BSE) and provided with a leaflet in the local language explaining the purpose and methodology of BSE.

Women in the control area received no active intervention, but were exposed to the general health education campaigns carried out by municipal authorities and voluntary bodies.

The examiners were trained using a program already developed and tested in the Philippines, making use of breast silicon models. Training was repeated for selected groups of examiners with detection rates markedly above or below the mean. Women eligible for screening were invited to participate through a variety of mechanisms but mainly by home visits.

At the first visit women were interviewed to record demographic variables and risk factors for breast cancer. Instruction in BSE was given and PE performed. Demographic characteristics of women who refused PE were also recorded.

Women with detected abnormalities were referred for final diagnosis to special clinics, made available in 3 major hospitals staffed by project personnel.

After one year of intervention, compliance with referral was only 21% and all remedies put in place to improve it (see below), did not significantly affect the proportion of positive women who reached a definitive diagnosis.

The intervention was therefore discontinued after the completion of the first round and follow-up of the intervention and control cohorts has been undertaken.

The follow-up phase has been undertaken.

Results

A) Intervention

During 1995 a coordinating center was set up. Two hundred and two Health Centers were randomized to intervention and control arms. Hospital clinics for referral of positive women and mechanisms for documentation of results were established.

Personnel from the intervention HCs were recruited and trained. It soon became evident that the regular personnel of HCs could not reach the scheduled rate of 14,000 woman-examinations per month. Therefore, nurses were recruited to work full-time for the project (FTNs). In March 1996, the intervention reached a regular pace. The first round of the intervention was completed in December 1997. The results of the intervention after completion of the single round of examinations, are summarized in table 1. Three-thousand four hundred and ninety two women were detected positive for a lump at first examination. Of these, 42.3% actively refused further investigation, 21.8% who did not report to the tumor clinics had moved away or died when visited at home and seventy-one cases (2%) are waiting for final diagnosis. Only 32% (1,110 women) completed the diagnostic process, of these 33 were malignant cancers detected.

Comparison of characteristics of compliers and refusers.

In the annual report of 1997 we presented an analysis of the characteristics of a sample of women who accepted PE and of those who refused it. The two groups do not differ by age, prevalence of smoking or compliance with screening for cervix cancer, the latter being an indication of general attitude towards preventive practices. In contrast with what is observed in western countries, refusers are of higher social class, as indicated by greater average income and significantly lower parity.

Action taken to improve compliance with clinical investigation among women detected positive.

One thousand women who were positive for a lump at the initial visit but who had not subsequently turned up at a referral clinic were visited a second time to assess the motives for non-compliance. The survey indicates that the main reasons for non-compliance are inconvenience and costs. In order to induce greater motivation to seek medical attention, medical teams formed by a doctor and a nurse and equipped to perform needle biopsies, were sent to visit non-compliers at home in order to obtain a final diagnosis. This activity commenced in March 1997 (recruitment and training of doctors) and was completed by end of April 1998. The results of active clinical follow up are also summarized in table 1.

B) Modification of study protocol and plan of work

The experience of the first 2 years of field activity indicates that a screening program by PE can attain high coverage in this urban population. The positivity rate (3.0%) is sufficiently low to make this type of intervention cost-effective provided that the positive predictive value and sensitivity of the test prove to be high. At present, the positive predictive value of the screening test appears rather low but a definitive value will be available only when all incident cases will be identified and linked to the cohort. Sensitivity will be estimated eventually by comparing the incidence of interval cancers (not detected by screening) in the intervention group, with the incidence in the control group. The cancer registries will provide these data.

Revision of study protocol.

In October 1997 we submitted a revision of the study protocol which was accepted by the US Army Medical Research Command. The revision of the study concerns essentially discontinuation of the intervention after completion of the first round and undertaking of follow up of the target population. This will provide information on the effectiveness of the prevalent screen (incidence and mortality rates in the two groups), as well as identifying the risk factors for breast and other female cancers in this population. No analytical study has ever been conducted to explain the relatively high incidence of breast cancer in this population. The information collected by interview at time of the intervention will allow us to quantify the excess incidence attributable to known risk factors.

The cohorts (intervention and control) will be followed for up to 10 years to study the onset of breast cancer and resulting mortality in relation to screening. The association between reproductive factors and cancer of the breast has never been studied in a prospective study of this size in a population with fertility rates characteristic of developing countries but showing patterns of cancer risk quite high for Asian standards. Other cancer sites, which will be related to reproductive factors, tobacco smoking,

alcohol consumption and family history of cancer are cervix, ovary, corpus uteri, colon, lung, kidney and gallbladder. Cancers of the kidney and gallbladder have been associated with parity in women however, being rather rare cancer sites, the association has been investigated only in small studies. Details on this aspect of the study are given in the protocol revision and previous annual report.

C) Follow-up phase.

The follow-up of the intervention and control cohorts consists in identifying women who develop breast cancer and/or other cancers, those who die from other causes and those who migrate outside the study area. The databases are continuously updated and data analyses are performed at fixed "closing dates".

Most of 1998 was devoted to the clinical follow-up and management of women positive for a lump. The development of follow-up procedures and completion of databases from the intervention phase was also undertaken.

D) October 1998 - September 1999 achievements.

D.1 Completed activities.

Data entry, checking and cleaning of several databases, which will be the bases for the follow up and evaluation of the intervention have been completed. A summary description of these files is given in table 2.

Procedures to computerize the data collected on incident cases and death certificates have been established and regular data entry ensures the maintenance of these databases. Data entered are subject to systematic checks for errors of coding and typing and for inconsistencies in the information recorded.

Follow-up procedures to match the master file and lists of the eligible populations (intervention and control cohorts) with the files of newly diagnosed cases and death certificates have been developed and are performed regularly. This take advantage of a software program developed in Lyons for the purpose of identifying records pertaining to the same woman. The program makes use of the usual basic demographic items - names and surname, date of birth, age and detailed address - and allows for differences in spelling, or variations in the reported date of birth. Each variable contributing to the matching process is assigned a weight, which summarizes its discriminating power and the likelihood that it is reported incorrectly. The resulting matching score allows linkage of records within the same file (e.g. two screens of the same woman) or in different files.

The master file of the cohort of women examined at least once is being matched with the list of the population resident in the intervention areas in May 1997.

D.2 On-going activities.

D.2.1 Continuing identification and recording of new breast cancer cases diagnosed in the resident population. The distribution of 1,014 new cases diagnosed in 1995-1998 (61% of the total) by stage at diagnosis is shown in table 3. The table shows a small but significant reduction in stage IV disease and increase of stages I and IIA, in years 1997-98 compared to the previous two-year period.

D.2.2 Continuing collection of death certificates (all causes) of women aged 30+ and resident in Metro Manila.

D.2.3 Interview of a sample of 1,000 women resident in the control area.

A sample of 2,000 names, stratified by age, has been drawn from the file of the eligible population in the control HCs. Two interviewers have been recruited and trained to trace and perform interviews according to the questionnaire used in the intervention phase. Interviews are on-going and will continue

until completion of 1,000 questionnaires. Interviewers were provided with many more suitable names to allow for the turn-over of the resident population (migrated or deceased). The purpose of this sample survey is to estimate the actual proportion of the control cohort that is present in early 1999, and to compare the characteristics of this cohort with those of the intervention group as a check on the randomization procedure.

By August 1999, 678 interviews had been carried out.

D.2.3 Second attempt to improve compliance of positive women with clinical follow-up.

Forty-three percent of the 3,472 women detected positive for a lump at 1st examination, refused biopsy and further clinical investigations. A second attempt to motivate these women towards diagnosis and treatment if required, is being performed. Individual follow-up of these women has been organized. Women are contacted by nurses and offered a new examination by a doctor. The visits take place in the Health Centers of the women's residence.

D.2.4 Follow-up to assess vital status of intervention and control cohorts.

The file of death certificates is matched with the files of intervention and control population lists to identify women who died in the period. Unmatched women include those alive and resident but also some who migrated or died outside the area of Metro Manila. Active follow-up of this subgroup of the cohorts has to be performed at regular intervals.

The efficiency of different means to assess vital status of the women belonging to the study cohorts is being tested. A questionnaire will be mailed to a sample of 500 women to assess response rates. The sample is stratified by age and health center to account for differences in the socio-economical level of the women. Contacts by telephone will also be attempted.

The first systematic update of vital status is planned for year 2000.

(7) KEY RESEARCH ACCOMPLISHMENTS

- Impact of the intervention by PE on mortality from breast cancer.
- Risk of cancer of breast, colon, rectum, gallbladder, kidney, cervix and corpus uteri, ovary and thyroid in relation to several characteristics of women's reproductive life, obesity, height, alcohol consumption, family history of breast cancer and tobacco smoking.
- The same factors above plus education and socio-economical level as determinants of stage at diagnosis of breast cancer and survival, taking account of treatment received.
- All-causes mortality in women according to alcohol consumption, adjusting for social class and other factors.
- Determinants of compliance with early diagnosis and treatment in a developing country.
- Sensitivity of PE performed by trained nurses compared with doctors.

(8) REPORTABLE OUTCOMES

- Poster presentation at the Era of Hope Conference, Washington D.C., 1-4 October 1997.
- REC-LINK software program – for automatic matching of records based on personal id-items (e.g. name, surname, age, date of birth, address).
- Data base of the female population resident in Metro Manila in years 1995-1996.
- Data base of new cancer cases diagnosed in the resident population 1990-1998.
- Data base of breast cancer cases with clinical details of stage at diagnosis and initial treatment.

(9) CONCLUSIONS

The program as a whole is not expected to reduce mortality from breast cancer in this population due to the low compliance with clinical investigation and treatment of women found positive at PE. All remedies put in place to overcome, at least, logistical problems linked to referral failed to improve the compliance.

A shift in the distribution of stage at diagnosis towards earlier disease has been observed in cases diagnosed in the years when the intervention was carried out. Whether this is the result of the intervention is too early to tell but could be an indication of a potential positive impact of PE if accompanied by appropriate treatment.

During the first year of follow-up, the cancer registries have identified breast cancer cases presenting with advanced disease, who were positive at PE and refused further investigation one-two years earlier. This suggests that a small breast lump, which does not cause distress, is not perceived as something threatening one's health; it is only when the disease affects other organs that the woman seeks medical attention. This indicates that priority should be given to information and education of the population on the potential benefit of early detection. A better understanding of the cultural determinants of the attitude of this population towards health practices would help the Department of Health in developing future strategies.

The cohorts will be followed up for 5-10 years to study the onset of breast, other cancers and resulting mortality in relation to screening and to the data collected at interview during the initial examination. The association between reproductive factors and cancer of the breast has never been studied in a prospective study of this size in a population with fertility rates characteristic of developing countries but showing patterns of cancer risk quite high for Asian standards. Cancers of the kidney and gallbladder are associated with parity and obesity in women however being rather rare cancers the association has been investigated only in small studies. The cohort of this study offers therefore a unique opportunity to test the association.

Table 1.
Results of the single round screening, completed in December 1997.

Intervention		
No. interviewed	153,869	
No. interviewed and examined	147,558	
Compliance		96%
<hr/>		
Women detected positive		
Number of women detected positive and referred to tumor clinics	3,492	
positivity rate:		2.4%
No. referred who completed the diagnostic process:	1,110	
percent compliance (includes women visited at home):		31.8%
of which, No. referred who did not attend clinic and were visited at home	631	
No. with final diagnosis among women visited at home:	585	93.7%
<hr/>		
Outcome of diagnoses (3,492 women):		
no mass	545	15.6%
malignant breast cancer:	33	0.9%
benign breast disease:	532	15.2%
actively refused further investigation (at clinics or home visits):	1,476	42.3%
attended other clinic:	73	2.1%
pending diagnoses:	71	2.0%
not traced at initial address or died:	762	21.8%

Table 2. Description and size of the databases completed as a result of the intervention and of those maintained for the follow-up of the cohorts.

Intervention:

File	Content	No. of records
Master file	Nominal list of all women interviewed and offered PE. Includes 10% who refused PE	153,869
Referrals	Nominal list of all women detected positive at 1 st PE by nurses. This file contains also the details of clinical follow up and final diagnosis.	3,492
Intervention population lists	Lists of the eligible population resident in the intervention HCs in the years when the intervention was conducted.	218,928
Control population lists	Lists of the eligible population resident in the control HCs in the years when the intervention was conducted.	191,086
Repeated exams	Outcome of two examinations performed a year apart in a subgroup of the intervention cohort.	3,000
Control interviews	Interviews of a sample of 1,000 women resident in control HCs. (On-going)	678 provisional

Follow-up, performed by the two cancer registries:

Breast cancer cases	Detailed information on diagnoses (date, base and morphology if available), stage and survival of all new breast cancer cases diagnosed in Metro Manila.	1,700
Death Certificates	File of all deaths occurring in the resident population (women, age 30+) irrespective of the cause	3,864
All cancer cases	Basic information on diagnosis and survival of all malignant cancer cases diagnosed in the resident population.	years 1995-1997 6,163

Table 3 Relative frequency of stage at diagnosis of 1,014 incident cases by year of incidence, out of a total of 1,667 new cases identified. Stage has not been determined yet for 653 of the cases. Stage is defined according to the American Joint Committee on Cancer and UICC/TNM classification systems.

year of diagnosis	stage at diagnosis							
	0	I	IIA	IIB	IIIA	IIIB	IV	
1995	0.7	4.0	20.5	28.7	11.9	16.2	18.2	100
1996	0.7	4.7	20.1	26.6	14.2	16.8	16.8	100
1997	0.4	7.9	28.3	21.7	14.2	14.2	13.4	100
1998	0.0	6.6	22.4	31.1	12.0	16.9	10.9	100
95-96	0.7	4.3	20.3	27.7	13.0	16.5	17.5	100
97-98	0.2	7.3	25.9	25.6	13.3	15.3	12.4	100
<i>No. of cases</i>	<i>5</i>	<i>57</i>	<i>230</i>	<i>272</i>	<i>133</i>	<i>162</i>	<i>155</i>	<i>1,014</i>

(10) REFERENCES

Barnum, H. and Greenberg, R. (1991) Health Sector Priorities Review. Cancer. The World Bank, Washington, D.C.

Coleman, M.P., Estève, J., Damiecki, P., Arslan, A. and Renard, H. (1993) Trends in Cancer Incidence and Mortality (IARC Scientific Publications No. 121), Lyon, International Agency for Research on Cancer.

Day, N.E. (1991) Screening for Breast Cancer. *Brit Med Bull* **47**, 400-415.

Ferlay J., Parkin D.M., Pisani P., GLOBOCAN 1, IARC Cancer Base No.3, 1998, IARC, Lyons.

Miller, A. B., Chamberlain, J., Day, N.E., Hakama, M. and Prorok, P.C. (1990). Report on a workshop of the UICC project on evaluation of screening for cancer. *Int J Cancer* **46**, 761-769.

Moss, S.E. (1996) Advances in screening for breast cancer. In: A.B. Miller (ed.) *Advances in cancer screening*. Kluwer Academic Publishers, Norwell, USA.

Nab H.W., Hop W.C.J., Crommelin M.A., Kluck H.M., van der Heijden L.H., Coebergh J.W.W. (1994) Changes in long term prognosis for breast cancer in a Dutch cancer registry. *Br. Med.J.* **309**, 83-86.

Nelson N.J. (1997) The mammography consensus jury speaks out. *J.Natl. Cancer Inst.* **89**,344-347.

Olivotto I.A., Bajdik C.D., Plenderleith I.H.,Coppin C.M., Gelmon K.A., Jackson S.M., Ragaz J., Wilson K. S., Worth A. (1994) Adjuvant systemic therapy and survival after breast cancer. *N. Engl. J. Med.* **330**, 805-810.

Pisani P, Parkin D.M., Muñoz N., Ferlay J. (1997) Cancer and infection, estimates of the attributable fraction in 1990. *Cancer Epidemiol. Biomarkers & Prev.*

Thomas B.D., Gao D.L., Self S.G., Allison C.J., Tao Y., Mahloch J., Ray R., Qin Q., Presley R., Porter P. (1997) Randomized trial of breast self-examination in Shanghai: methodology and preliminary results. *J.Natl. Cancer Inst.* **89**, 355-365.

WHO (1984) Self-examination in the early detection of breast cancer: memorandum from a WHO meeting. *Bull WHO* **62**, 861-869,